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Mathematical Models of the Use of Caffeine as a Counter Measure to the Deterioration of Neurobehaviorial Functioning During Sleep Deprivation

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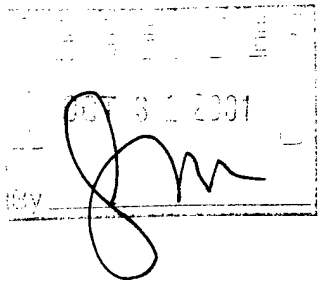
13. ABSTRACT (Maximum 200 words)

The specific aims are to refine mathematical models that predict homeostatic and circadian regulation of human alertness and short-term memory during sleep deprivation, and to validate these models using data from sleep deprivation studies. Then use these models to see the effects of low-dose, frequent use of caffeine. Work still needs to be done to achieve these aims.



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1. List of Manuscripts:

a. **Jewett ME**, Dijk D-J, Kronauer RE, Czeisler CA. Sigmoidal decline of homeostatic component in subjective alertness and cognitive throughput. *Sleep*, 1999, 22:S94-S95.

b. **Jewett ME**, Wyatt JK, Ritz-De Cecco A, Dijk D-J, Khalsa SB, Czeisler CA. Cognitive throughput and subjective alertness after awakening: investigation of sleep inertia with respect to three different circadian phases. *Sleep*, 1999, 22:S88-S89.

c. Khalsa SBS, **Jewett ME**, Cajochen C, Czeisler CA. A phase response curve to shifts of the sleep/wake schedule in humans. *Internat. Cong. on Chronobiology*, 8/21-9/1/99, Washington, D.C.

d. Ritz-De Cecco A, **Jewett ME**, Wyatt JK, Kronauer RE, Czeisler CA, Dijk D-J. Plasma melatonin rhythm in humans during a 20-h forced desynchrony protocol. World Federation of Sleep Research Societies conference, Dresden, Germany. October, 1999.

e. **Jewett ME**, Borbély AA, Czeisler CA. Editorial: Biomathematical modeling workshop, May 18-21, 1999. *J. Biol. Rhythms* 1999;14:429-430.

f. **Jewett ME**, Forger DB, Kronauer RE. Revised limit cycle oscillator model of the human circadian pacemaker. *J. Biol. Rhythms* 1999;14:493-499.

g. Kronauer RE, Forger DB, **Jewett ME**. Quantifying human circadian pacemaker response to brief, extended and repeated light stimuli over the photopic range. *J. Biol. Rhythms* 1999:14:500-515.

h. Forger DB, **Jewett ME**, Kronauer RE. A simpler model of the human circadian pacemaker. *J. Biol. Rhythms* 1999:14:532-537.

i. **Jewett ME**, Kronauer RE. Interactive mathematical models of subjective alertness and cognitive throughput in humans. *J. Biol. Rhythms* 1999;14:588-597.

j. Dijk D-J, **Jewett ME**, Czeisler CA, Kronauer RE. Reply to technical note: nonlinear interactions between circadian and homeostatic processes: models or metrics? *J. Biol. Rhythms* 1999;14:604-605.

k. Klerman EB, **Jewett ME**. Commentary: Model building, quantitative testing and model comparison. *J. Biol. Rhythms* 1999;14:621-624.

l. Benke KS, **Jewett ME**, Kalsa SBS, Czeisler CA. Hourly and 30-minute sampling: similar phase estimates for plasma melatonin. Abstracts, Northeastern Sleep Society Mtg. 2000; (in press).

m. **Jewett ME**, Khalsa SBS, Klerman EB, Duffy JF, Rimmer DW, Kronauer RE, Czeisler CA. 3-cycle bright light stimulus induces type 0 resetting in human melatonin rhythm. Abstracts. 7th mtg, Society for Research on Biological Rhythms. 2000;(submitted).

n. Benke KS, **Jewett ME**, Kalsa SBS, Czeisler CA. Decreased sampling rates may provide acceptable melatonin phase, duration and amplitude estimates, depending on the precision required. Abstracts, 7th mtg, Society for Research on Biological Rhythms, 2000;(submitted).

o. Khalsa SBS. **Jewett ME**, Cajochen C, Czeisler CA. A phase response curve to single pulses of bright light in humans. *Sleep* 2000; (in press).

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2. Scientific Personnel:

Name: **Megan E. Jewett, Ph.D.**

Honors/Awards/Degrees received:

Research Merit Travel Award, American Professional Sleep Societies

Trainee Research Excellence Award. American Professional Sleep Societies

3. Report of Inventions:

None.

4. Scientific Progress and Accomplishments:

4a. Organized International Modeling Workshop. During this reporting period. the Principal Investigator, Dr. Megan E. Jewett, organized an international workshop entitled *Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans*, which was held at the MIT Endicott Center on May 19-21, 1999. In coordination with the workshop co-chairs (Drs. Czeisler and Borbély), Dr. Jewett established the workshop's primary goals, secured funding for the workshop. selected appropriate invitees, created a travel scholarship fund for students, organized the workshop schedule, and coordinated all travel, housing and meals for the attendees. Forty-five international experts in the field attended. The workshop was highly successful. resulting in twenty-three manuscripts that were published in a special issue of the *Journal of Biological Rhythms*, in December, 1999 (see below).

4b. Guest Edited Special Issue of *JBR* Dedicated to Modeling. The proceedings of the workshop on *Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans* (see above) were published in a special issue of the *Journal of Biological Rhythms*, in December. 1999, edited by Drs. Jewett, Czeisler and Borbély. Dr. Jewett organized the structure of the journal issue. edited all manuscripts, reviewed all proofs, and secured funding for the printing of color figures where necessary.

4c. Scored Subjective Alertness and Cognitive Throughput Data. During this reporting period, a standardized method was developed for the editing, coding and scoring of neurobehavioral data from 16 subjects who participated in a 29-day study of the effects of sustained low-dose caffeine administration on performance and alertness at different circadian phases and after different lengths of wakefulness. While still blind to the drug condition (placebo vs. caffeine), cognitive throughput data (measured using an addition task) and subjective alertness data (measured using a visual analog scale) were then edited, coded and scored according to the standardized method developed. This provided us with data from approximately 5,050 addition tests and 13.800 subjective alertness tests collected across the circadian cycle for lengths of wakefulness up to 29 hours. During the next reporting period. these data will be used to refine our current mathematical models of cognitive throughput and subjective alertness.

4d. Developed a Preliminary Model of PVT Lapses. Because during the current reporting period we were still blind to drug condition in the data collected from our caffeine study, data from the laboratory of Dr. David Dinges at Pennsylvania Medical School were used to develop a preliminary mathematical model to predict the effects of circadian phase and sleep/wake history on psychomotor vigilance (measured using a psychomotor vigilance task, PVT). In this model, we have changed the structure of our original equations representing the effects of sleep/wake history (Homeostat, *H*) and the effects of *H* on the amplitude of the circadian component (*C*) so that they better reflect our theoretical understanding of the nature of these components. Most notably, unlike our previous models. the slope of *H* at its peak is no longer zero, so that we no longer have to contend with a model that predicts no effect of wakefulness when the sleep need is completely satiated. The preliminary model for PVT lapses (reaction times > 500 msec) is shown below.

Circadian Component (C)

$$C = a + A_c(0.91x - 0.29x_c)$$

$$A_c = u_c \cdot \tanh\left(\frac{H}{h_{Ac}}\right)$$

Parameter Values: u_c = 5.84; h_{Ac} = 10.69;

(Note: x and x_c are derived from the model of the effects of light on the human circadian pacemaker described below in 4e.)

Homeostatic Component (H)

During wake, $$\dot{H} = r_{iw}\left[1 + \tanh\left(\frac{I - u_c}{r_{isw}}\right)\right]$$

During Sleep, $$\dot{H} = r_{isw}(1 - 0.1x)(u_{ic} - H)$$

Parameter Values: t_o = 16.05, r_{iw} = 6.64x10^{-2} h^{-1}, h_o = -31, h_i = 613, r_{isl} = 1/2.3 h^{-1}
u_c = 0.955

Sleep Inertia Component (W)

During wake, $$\dot{W} = -r_w W$$

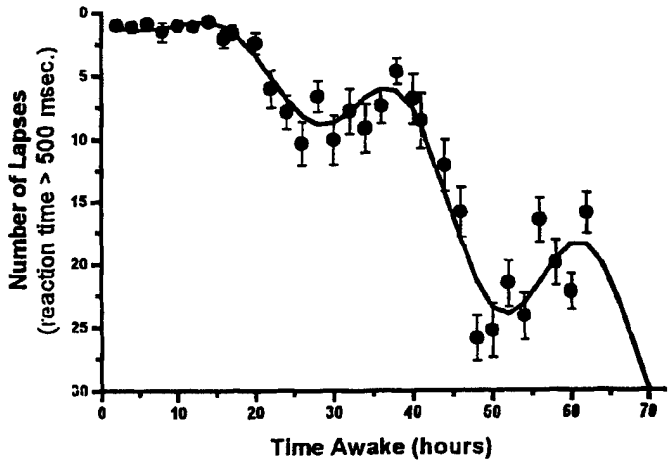
During sleep, For $H + C \geq |W_c|$, $W = W_c$
For $H + C < |W_c|$ $W = -(H + C)$

Parameter Values: r_w = 1/0.79 h^{-1}; W_c = -0.5346

PVT Lapses (L)

$$L = C + H + W$$

This preliminary model of PVT lapses (see figure. solid line) is able to predict actual PVT lapses observed during 64 hours of total sleep deprivation (see figure, solid circles) quite well. In the next reporting period we will focus on the homeostatic recovery function during sleep.



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4e. Refined Mathematical Model of the Effects of Light on the Human Circadian Pacemaker. During the reporting period, we further refined our mathematical model of the effects of light on the human circadian pacemaker, resulting in three publications (see references f-h in the publication list above). The majority of these refinements involved estimating parameter values with a higher level of precision. The details of this work is thoroughly described in the published manuscripts.

5. Technology Transfer:

None.

The Timing of the Human Circadian Clock is Accurately Represented by the Core Body Temperature Rhythm Following a Light-induced Phase Shift Near the Critical Zone

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Key Words

circadian, rhythm, light, phase shift, clock, human

Abstract

A double-pulse experiment was conducted to evaluate the phase of the underlying circadian clock following light-induced phase shifts of the human circadian clock. Circadian phase was assayed from the rhythm in core body temperature before and after 3-cycle bright light stimuli applied near the estimated minimum of the core body temperature rhythm. The phase shifts following identical consecutive light stimuli were compared with phase shifts obtained in a previous study for light stimuli at similar circadian phases. Phase shifts to consecutive stimuli were no different from those following stimuli applied under steady-state conditions. These data suggest that circadian phase shifts to a 3-cycle stimulus, as measured from the core body temperature rhythm, occur within 24 hours following the light stimulus and accurately reflect the timing of the underlying circadian clock.

10/9/1999

REVISED LIMIT CYCLE OSCILLATOR MODEL OF HUMAN CIRCADIAN PACEMAKER

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14 pages, 6 figures
Running Title: HUMAN CIRCADIAN PACEMAKER MODEL

Abstract

In 1990, Kronauer proposed a mathematical model of the effects of light on the human circadian pacemaker. We present here several refinements to Kronauer's original model of the pacemaker that enable it to more accurately predict the experimental results from a number of different studies of the effects of the intensity, timing and duration of light stimuli on the human circadian pacemaker. These refinements include the following:

(i) The van der Pol oscillator from the original model has been replaced with a higher-order limit cycle oscillator so that the system's amplitude recovery is slower near the singularity and faster near the limit cycle;

(ii) The phase and amplitude of the circadian rhythm in sensitivity to light from the original model has been refined so that the peak sensitivity to light on the limit cycle now occurs ~4 hours before the core body temperature minimum (CBT_{min}) and is three times greater than the minimum sensitivity on the limit cycle.

(iii)The critical phase [at which type 1 phase response curves (PRCs) can be distinguished from Type 0 PRCs] that occurs at CBT_{min} now corresponds to 0.8 h *after* the minimum of x (x_{min}) in this refined model, rather than to the exact timing of x_{min}, as in the original model.

(iv) A direct effect of light on circadian period was incorporated into the model such that as light intensity increases, the period decreases, which is in accordance with 'Aschoff's rule'.

The refined model fits current data sets quite well, and generates the following testable predictions:

(i) It should be difficult to enhance normal circadian amplitude via bright light.

(ii) Near the critical phase, the slopes of type 0 PRCs should be steeper than the slopes of type 1 PRCs.

(iii) Human PRCs to bright light will have larger regions of initial phases that induce phase delays than regions that induce phase advances, even after correcting for drift between phase assessments due to a non-24-hour circadian period.

(iv) Circadian period measured during forced desynchrony experiments should be directly affected by ambient light intensity during waking, with brighter intensities generating shorter observed periods.

10/09/99

QUANTIFYING HUMAN CIRCADIAN PACEMAKER RESPONSE TO BRIEF, EXTENDED AND REPEATED LIGHT STIMULI OVER THE PHOTOTOPIC RANGE

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20 pages, 11 figures

Running Title: Quantifying Human Circadian Response to Light

Abstract

While our previous models have been able to accurately describe the effects of extended (~5 h) bright light (>4000 lux) stimuli on the phase and amplitude of the human circadian pacemaker, they are not sufficient to represent the surprising human sensitivity to both brief pulses of bright light and light of more moderate intensities. We have therefore devised a new model in which a dynamic stimulus processor (*Process L*) intervenes between the light stimuli and the traditional representation of the circadian pacemaker as a self-sustaining limit-cycle oscillator (*Process P*). The overall model incorporating *Process L* and *Process P* is intended to allow the prediction of phase shifts to photic stimuli of any temporal pattern (extended as well as brief light episodes) and any light intensity in the photopic range. Two time constants emerge in the *Process L* model: the characteristic duration of the bright light pulses necessary to achieve their full effect (5-10 min), and the characteristic stimulus-free (dark) interval that can be tolerated without incurring an excessive penalty in phase shifting (30-80 min). The effect of reducing light intensity is incorporated in *Process L* as an extension of the time necessary for the light pulse to be fully realized (a power-law relation between time and intensity). This new model generates a number of new testable hypotheses, including the surprising prediction that 24h cycles consisting of 8 h of darkness and 16 h of only ~3.5 lux would be capable of entraining a large fraction of the adult population (~50%). Experimental data on the response of the human circadian system to lower light intensities and briefer stimuli are needed to allow for further refinement and validation of the model we propose here.

A SIMPLER MODEL OF THE HUMAN CIRCADIAN PACEMAKER

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18 Pages, 3 Figures

Abstract

Numerous studies have used the classic van der Pol oscillator, which contains a cubic nonlinearity, to model the effect of light on the human circadian pacemaker. Jewett and Kronauer (1998) demonstrated that Ashoff's rule could be incorporated into van der Pol type models, and used a van der Pol type oscillator with higher-order nonlinearities. Kronauer, Forger and Jewett (1999) have proposed a model for light preprocessing, *Process L*, representing a biochemical process that converts a light signal into an effective drive on the circadian pacemaker. In this short report, we use the classic van der Pol oscillator with *Process L* and Jewett and Kronauer's (1998) model of Ashoff's rule to model the human circadian pacemaker. This simpler cubic model predicts the results of a three-pulse human phase response curve experiment and a two-pulse amplitude reduction study with as great, or greater, accuracy as the models of Jewett and Kronauer (1998) and Kronauer, Forger and Jewett (1999) which both employ a nonlinearity of degree 7. This suggests that this simpler cubic model should be considered as a potential alternative to other models of the human circadian system current available.

Introduction

Since the mechanism of the human circadian pacemaker is known only incompletely, mathematical models that accurately describe overt circadian behavior and responses to various stimuli can be used both to understand the human circadian system in functional terms and to inform further studies on basic mechanisms. Jewett, Kronauer and Czeisler (1994) have shown that the human circadian pacemaker acts as a limit cycle

Commentary: Model Building, Quantitative Testing and Model Comparison

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Running title: Model Building, Testing and Comparison

Keywords: model, circadian rhythms, neurobehavioral testing, mathematical models, statistics

This workshop on biomathematical models was designed for the presentation and discussion of current models of circadian rhythmicity, sleep regulation and neurobehavioral function in humans. When multiple models are presented, comparison occurs naturally, even if not formally. However, as many researchers have emphasized, it is important to formally compare mathematical models against other potential model structures, experimental and/or field data, and other published models.

Throughout the entire process of scientific inquiry culminating in the development of mathematical models, it is important to include the comparison of possible alternative models. At step in the process, all potential models should be considered; no one model should be chosen without first exploring the alternatives. The scientific method itself is based upon the comparison of different hypotheses, which often represent alternative models of a system. The process of designing and performing an experiment involves a consideration of mental models of the system under study. Even the process of statistically analyzing data requires choosing a model to represent the underlying processes of the data (e.g., see (van Dongen et al., 1999)). Finally, when formulating a mathematical model to describe an underlying system, it is important to consider many alternative mathematical systems before choosing the final set of equation types. Thus, this commentary will explore some of the issues involved in preparation and comparison of mathematical models of circadian and neurobehavioral systems.

Approaches to modeling: the direct and inverse problems

In the current issue, Brown and Luithardt (Brown and Luithardt, 1999) elegantly describe two different kinds of mathematical modeling methods and discuss how to use a combination of these to generate new models. The first method is the "direct problem": begin with a model

EXPOSURE TO A CRITICAL BRIGHT LIGHT STIMULUS CAN SUPPRESS THE ENDOGENOUS CIRCADIAN AMPLITUDE OF THE MELATONIN AND TEMPERATURE RHYTHMS IN HUMANS

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RUNNING TITLE: Melatonin rhythm amplitude reduction

ABSTRACT

Strong type 0 circadian phase resetting, characterized by the association of substantial reduction of circadian amplitude with the largest magnitude phase shifts, has been described in response to light in single celled organisms, insects and plants. However, higher organisms such as mammals were thought to be incapable of such strong resetting until it was reported in humans ten years ago. A major issue in the ensuing debate over this finding has been whether a light stimulus of critical strength applied at a critical phase can lead to amplitude suppression of the human circadian pacemaker, as predicted for a phase-amplitude oscillator capable of strong type 0 resetting. A prior report of profound circadian amplitude attenuation in humans (i.e., "stopping the clock") has been questioned due to discordance in some cases between the amplitude suppression observed in the two output rhythms measured, core body temperature and plasma cortisol. We have therefore assessed the response of the pineal hormone melatonin—the rhythmic release of which is known to be driven directly by the human circadian pacemaker—to a light stimulus designed to attenuate circadian amplitude. Endogenous circadian phase and amplitude of the melatonin and temperature rhythms were assessed in seven men using data from constant routines conducted before and after light stimuli first timed to drive the circadian system near its singular region, which is characterized by amplitude reduction, and then timed to restore circadian amplitude.

We found that amplitudes of both the melatonin and temperature rhythms could be suppressed by light, and that their relative amplitudes remained highly correlated, suggesting that they reflect an attenuation in the oscillation amplitude of the hypothalamic circadian pacemaker. These data support the concept that the human pacemaker is indeed capable of strong type 0 circadian phase resetting in response to light. They also indicate that at least two state variables, such as phase and amplitude, are required to describe mathematically the human circadian pacemaker and its resetting responses to light.

Key words: melatonin, temperature, phase shifts, amplitude, bright light, suprachiasmatic nucleus, phase-response curve, circadian rhythms, human

MEJ

INTERACTIVE MATHEMATICAL MODELS OF SUBJECTIVE ALERTNESS AND COGNITIVE THROUGHPUT IN HUMANS

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18 Pages, 4 Figures

Abstract. We present here mathematical models in which levels of subjective alertness and cognitive throughput are predicted by three components that interact with one another in a non-linear manner. These components are: 1) a homeostatic component (H) that falls in a sigmoidal manner during wake and rises in a saturating exponential manner at a rate that is determined by circadian phase during sleep, 2) a circadian component (C) that is a function of the output of our mathematical model of the effect of light on the circadian pacemaker, with the amplitude further regulated by the level of H, and 3) a sleep inertia component (W) that rises in a saturating exponential manner after waketime. We first construct initial models of subjective alertness and cognitive throughput based on the results of sleep inertia studies, sleep deprivation studies initiated across all circadian phases, 28-h forced desynchrony studies, and alertness and performance dose response curves to sleep. These initial models are then refined using data from nearly one hundred and fifty 30- to 50-h sleep deprivation studies in which subjects woke at their habitual times. The interactive three-component models presented here are able to predict even the fine details of neurobehavioral data from sleep deprivation studies and, after further validation, may provide a powerful tool for the design of safe shiftwork and travel schedules, including those in which people are exposed to unusual patterns of light.